22 October 2015
EMA/684369/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the 'Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use' (EMA/CHMP/SWP/272921/2012)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Federation of Pharmaceutical Industries and Associations (EFPIA)
2	Association of the European Self-Medication Industry (AESGP)
3	Medicines Evaluation Board (MEB), The Netherlands
4	Eisai
5	Reckitt Benckiser Healthcare (UK) Ltd
6	SciencePharma (Poland)
7	David J Snodin, Xiphora Biopharma Consulting

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5505
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	EFPIA welcomes this CHMP/SWP science-based evaluation in support of safe levels for methyl and propylparaben. We agree it should address, and take away any concerns raised during the last decade by the scientific community, regulatory agencies and the general public as a consequence of perceived endocrine-disrupting effects. Without adequate preservation, products can pose serious health risks to consumers. Paraben esters are historically the most widely used preservatives with nearly 100 years of history of safe use in drugs, food and cosmetics. They preserve formulation without impacting the colour or odour, and are effective against a wide range of microorganisms over a broad pH range at low concentrations. They have undergone recent extensive review with various regulatory authorities (CIR, SCCS and EFSA). The evidence based SWP evaluation is especially welcomed by EFPIA to balance recent views on these well-characterised preservatives. In our view, it helps preventing industry from having to look at alternatives, with less defined safety profiles and that could introduce new hazards and risks for indispensable elements of a product formulation. Thus, EFPIA agrees overall with the proposed oral levels for named parabens, with the exception of the caveat made for use of propylparaben under the age of 2 years. Rationale: for children below 2 years, a PDE for propylparaben has not been set, because of the uncertainty about the metabolizing capacity at this very early age, and the absence of animal data corresponding to this age group. Thus, it is concluded that for children below 2 years, further exposure data for propylparaben are	The new study was taken into account during the revision of the reflection paper. It was actually performed in animals covering patients aged 0-2 years, and at relevant exposure levels. However, it was considered that the lack of estrogenic effect could not be ascertained at the high dose level in females.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	needed. An EFPIA member company has recently performed additional investigations to specifically fill this knowledge gap; the results show the absence of estrogenic effects for this age category and at relevant exposure levels and days of development. Enclosed is a presentation summarising the findings of these investigations. The official GLP report, to be finalised by the end of November 2013, will be made available to the EMA/CHMP/SWP for review at its earliest opportunity. Thus, EFPIA strongly recommends changing the aforementioned caveat regarding the propylparaben PDE to also include children of all ages.	
2	AESGP welcomes the opportunity of being consulted on this draft EMA reflection paper addressing methyl- and propylparaben used in oral pharmaceutical formulations especially in light of the fact that the EMA may propose an updated wording of parabens in the next revision of the "Guideline on Excipients in the Label and Package Leaflet of Medicinal Products for Human Use" (CPMP/436/00). As a general comment, AESGP would appreciate making greater reference to the Gazin et al study recently published in the official journal of the Society of Toxicology, Toxicological sciences (Impact factor: 4.328).	Results of Gazin et al (2013) were included appropriately in the document. The reference was updated since only an abstract was available when the draft reflection paper was published.
3	<u>General comment 1:</u> According to contents of this reflection paper, the purpose of this paper is to update the information on parabens (preservatives) for the	The title of the reflection paper mentions explicitly that it covers the use of methyl- and propylparaben as excipients in human medicinal products for oral use. And the introduction

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	medicinal package leaflet & labelling in the "*Guideline on excipients in the Label and Package Leaflet of Medicinal Products for Human Use" (CHMP/463/00)*", based on new scientific safety knowledge and assessment, of specifically methyl- and propylparaben in oral pharmaceutical products. (See section "Introduction" of reflection paper). However, the risk assessments and conclusions in this paper cover a wider scope than the labelling guideline. They focus on the question whether oral pharmaceutical products containing methyl- and/or propylparaben pose a safety risk, why, and at which dose levels (= B/R) (which we highly appreciate). The focus of the existing labelling guideline however, is on providing background on why the listed excipients may be a risk (e.g. allergic potential, etc.) at the stated level (in case of the parabens: "nul"). This wider scope of the paper should be highlighted and explained in the paper, e.g. by adding a section "scope". <u>Comment 2:</u> Given the wider scope of the paper, the consequences at Section "Conclusion" should be more specifically stated. The following is concluded in the paper: -"Methylparaben has not been associated with adverse effects....This allows concluding that the use of methylparaben in oral formulations up to 0.2% of the product (as within the recommended effective concentrations as a preservative) is not a concern for humans including the paediatric population whatever the age group.." and, -"..The use of a propylparaben containing formulation for the very young could be justified on a case-by-case basis from a benefit/risk	largely relies on their use as excipients. As regards any medicinal products containing these parabens as active substances at higher concentrations, they should be granted a marketing authorization if the benefits are judged to be greater than the risks. Therefore, they are not covered by this reflection paper.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	perspective, weighting the need for treatment against the potential risk. This assessment should take into account several factors such as the posology and concentration of propylparaben, the treatment duration, the severity of the disease and availability of alternative treatments. A PDE value of 5 mg/kg/day can be calculated for the use of propylparaben in adults and children older than 2 years with mature metabolic capacity...". The consequences of these conclusions for quality of paraben containing formulations should be stated. Comment 3: The paper does not mention the use of parabens as active ingredients. In the Netherlands there is at least one oral formulation, a lozenge (indication: sore throat), with propyl paraben as active ingredient. The dose is 1.8 mg/tablet, with a maximum of 8 tablets/day for adults and 6 tablets/day for children. So the total dose is 14.4 mg/day for adults and 10.8 mg/day for children, distributed over the day. This total dose is still far below the proposed PDE of 5 mg/kg/day, however the PDE is based on short-term exposure and this type of use can be expected to result in a more prolonged systemic exposure over time. If the use as active ingredient is not intended to be covered in the paper, this should be explicitly stated somewhere (at least in the introduction). Proposed change (if any): Explicitly state in the introduction that the paper only addresses the use as excipient and not the use of higher concentrations as active ingredient.	
4	Eisai appreciates the opportunity to provide comments on the	As indicated above, a new juvenile toxicity study was

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	'Reflection paper on the use of methyl- and propylparaben as excipients in human medicinal products for oral use' released by the EMA for public consultation. We generally welcome the proposals to allow the use of methyl- and propylparabens in human medicinal products for oral use. However, we have a few general comments about the use of propylparaben in human medicinal products for oral use that we would like to express. All these comments are detailed with proposed changes in the second part of this template. Our main comments are summarized below : • The SWP has expressed a concern about the use of propylparaben in human medicinal products for oral use in pediatric populations under 2 years of age based on a lack of information about the metabolic capacity in this population for the metabolism of parabens. **Recent knowledge in this field appears to give substantial support to the conclusion that the main enzyme system responsible for metabolism / hydrolysis of parabens esters are the carboxylesterases in humans (hCE1 and hCE2).** • The metabolic capacity and maturation of carboxylesterases in children 1-2 years of age is documented in the literature, and supports a proposed **PDE of 2.5 mg / kg / day** in this population.	performed with propylparaben in animals covering patients aged 0-2 years. A PDE of 2 mg/kg/day could be derived from this study. The reflection paper was updated accordingly.
5	The draft reflection paper cites Rowe et al (2006) with regard to percentage inclusion levels of methyl and propylparabens in human oral medicines. Reckitt Benckiser is aware of marketed medicinal products within Europe with levels above those stated in the reflection paper. Reckitt Benckiser has data that can be shared under	The SWP appreciates the proposal of Reckitt Benckiser but considers that the figures mentioned in the reflection paper should not be modified as explained thereafter. The reflection paper relies on Rowe et al (2012) to report ranges of concentrations of methyl- and propylparaben used

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	confidentiality to support the above assumption.	in human medicinal products. In fact, the use of both excipients could vary from one medicinal product to another. In any case, they should be used in line with the recommendations laid down in the "guideline on excipients in the dossier for application for marketing authorisation of a medicinal product" (EMEA/CHMP/QWP/396951/2006). Any excessive concentration should be justified. Therefore, relying on the data reported by Rowe et al (2012) is considered a reasonable approach since it represents the use of both excipients in most medicinal products.
6	• Mixture of methylparaben and propylparaben is one of the most commonly used preservation systems in the medicinal products. Usually methylparaben and propylparaben are not used separately in pharmaceutical formulations. The Reflection paper discusses each paraben separately and does not take into consideration the fact that parabens generally are used as a mixture. We propose to discuss in the Reflection Paper combinations of parabens. Reflection Paper should be supplemented with data which refers to mixture of methyl- and propylparaben. • In our opinion, the document should also consider the concentration of parabens in medicinal products dedicated to paediatric population under 2 years old.	No experimental data was found with such a combination. A comment on this issue is discussed later in this document.
7	The conclusion of the reflection paper is supported with some provisos. It is believed that additional information is available on propyl paraben to make a more robust evaluation and to provide reassurance on use of propyl paraben in infants. An assessment report (anonymised and written in 2011) is attached in order to provided background information on many of the points	No specific comment.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	made on the toxicological evaluation of propyl paraben by Oishi. A link to a general review of the safety issues on parabens follows: http://www.jle.com/e-docs/00/04/80/88/article.phtml	

2. Specific comments on text

[

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 32 - 35	6	Comments: This paragraph seems to be unnecessary in the final version of the document.	Not accepted. This paragraph explains the reasons underlying the need of a specific reflection paper on the use of parabens in medicinal products for oral use. A similar paragraph is also included in the "guideline on the use of phthalates as excipients in human medicinal products" adopted by the CHMP in November 2014.
Line 37	3	Comments: Suggestion: Should "allergic" be "allergenic"? <u>Proposed change (if any):</u> Allergenic (seems more correct, but final decision to be taken by EMA or author).	Accepted.
Lines 45 – 50	3	Comments: It would be helpful if the maximum dose of methylparaben and propylparaben received with existing oral formulations would be mentioned already in the introduction. Now only the maximum amount of propylparaben is mentioned at the end of the paper (line 286) and no maximum dose of methylparaben is mentioned. With this information it is easier for the reader to interpret NOELs and ADIs discussed in section 2 of the paper. <u>Proposed change (if any):</u>	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Addition of maximum dose of methylparaben and propylparaben in introduction.	
45-48	5	Comments: The data from Rowe et al (2006) are not fully representative of actual market usage of methyl and propyl parabens Proposed change (if any): Ranges/ratios to be amended to reflect market situation (Reckitt Benckiser have proprietary data that can be shared under confidentiality to support the above recommendation) Proposed change (if any):	Not accepted (see comment on this issue in section 1).
Line 48	3	Comments: “Rowe et al, 2006” is updated by a new version. Proposed change (if any): Update “Rowe et al, 2006” to “Rowe et al, 2013”.	Accepted (although it is noted that it is actually Rowe et al 2012).
Line 86	4	Comments: It is postulated that various types of esterases are responsible for the metabolism of parabens esters in humans. As reported in the literature, recent knowledge in this field appears to give substantial support to the conclusion that the main enzyme system responsible for metabolism/hydrolysis of parabens esters are the carboxylesterases in humans (hCE1 and hCE2) [1,2,3,4]. This allows the scientific community to consider what is known about how the expression and activity of these	Partly accepted. These papers report the significant involvement of carboxylesterases, notably hCE1 and/or hCE2 isoforms, in hydrolysis of parabens - they are expressed in many tissues, notably liver microsomes (hCE1>hCE2), colon and other extrahepatic tissues (mostly hCE2). Since parabens undergo intestinal metabolism and first pass effect in liver, it is acknowledged that involvement of these isoforms in their “initial” metabolism is considerable. However, Abbas et al (2010) also report that 50% of propylparaben incubated in human plasma was hydrolysed to 4-

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		enzymes changes with age in humans, thereby allowing for assessment the metabolic capacity in children under the age of 2 years old.  Harville et al 2007.pdf 1. Harville et al 2007  Abbas et al 2010.pdf 2. Abbas et al 2010  Jewell et al 2007.pdf 3. Jewell et al 2007  Jewell et al 2007a.pdf 4. Jewell et al 2007a <u>Proposed edits to the text</u>: ~~'Various types of esterases are~~ **Carboxylesterases** are **the main enzyme system** responsible for the **initial** metabolism of parabens…'	HBA after 24 hours, thus suggesting that esterases found in plasma may also metabolize this compound. They also underlie inter-individual esterase activity variation since a previous study showed that propylparaben was stable in similar conditions. Considering that esterase activity is maturing in the youngest patients, it seems preferable not to exclude the involvement of plasma esterases. Nevertheless, the wording was modified to highlight the preponderance of hCE1/2. "Various types of esterases, notably carboxylesterases hCE1 and hCE2, are responsible for the metabolism of parabens. Glucuronide and sulphonate esters are formed subsequently, via involvement of various enzymes."
Line 75	7	Comments: Additional data are available in the publication by Abbas et al, Drug Metab Pharmacokinet. 2010;25(6):568-77.	Not accepted (no change proposed).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 90 – 131 and 167.	3	Comments: According to the title of the reflection paper and the introduction, the document only addresses methyl- and propylparaben. However, in Sections 2.2 and 2.4 many unnecessary details (potency factors compared to E2) are included concerning other parabens, which makes the text inconvenient to read. Proposed change (if any): The text could be more conveniently arranged by summarising the information concerning the relation of estrogenic effect to chain length with ER affinity, potencies compared to E2 and effects in studies in a separate place, e.g. a separate section. In that case the main text could concentrate on the two parabens methyl- and propylparaben.	Partly accepted. The text was re-arranged to give ranges of affinity/ potency vs. E2 from methyl to butylparaben. Findings from Watanabe et al (2013 – cited in next comments) on the relation of estrogenic activity vs. chain length were also added. However, it was considered not to have different sections to report i) relationship between relation of estrogenic activity/ER affinity vs. chain length and ii) precise data on methyl- and propylparaben. This would drive some redundancy since it is relied on the same experimental data. Instead, the data obtained with methyl and propylparaben were tabulated (as suggested in next comments).
Lines 90 – 131 and 167.	3	Comments: It is not clear whether the cited potency factors compared to estradiol are ratio's of IC50 values, or of administered effect doses, or of ED50 ratio's. Based on the information provided in the paper, it is not possible to relate these potencies to actual doses or in vivo concentrations. Moreover, these potency estimates for uterotrophic effects in immature rats and mice are very variable, and also imprecise because generally they are based on only 1 tested estradiol dose/study (see Boberg et al). For reliable potency ratio's full dose response	Accepted. IC_{50} and EC_{50} values determined in *in vitro* studies were added to the text (whenever possible), at least for the positive control used in the study. As regards *in vivo* uterotrophic assays, it is necessary to provide some data comparing the tested parabens and the positive control (E_2 on most occasions) on a quantitative basis. ED_{50} values were calculated in only one publication testing methyl, ethyl, propyl and butylparaben in mice (immature, OVX) and immature rats (Lemini et al, 2003). Although reporting these values in the paper would not reflect the majority of the data set, it is noted that the lowest LOELs were determined by Lemini et al

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		curves are needed. For these reasons it would be preferable to add the actual absolute parameters (IC50, ED50 values) to the text, or even replace all potency factors by these values. Proposed change (if any): It is proposed to replace the factors by the actual results (IC50 values, ED50 values in comparison to maximum systemic concentrations c.q. maximum human dose)	(2003). In addition, positive results with these compounds were mostly obtained by Lemini et al (2003, 2004). Therefore, it is considered adequate to delete the former potency factor and replace them with ED_{50} values and/or paraben-to-E2 ED_{50} ratios (range from 2,000 to 30,000).
Lines 90-105	3	Comments: Lack of actual data. Proposed change (if any): Add IC50 data of methyl- and propylparaben to the text. Could also be done in the form of a table.	Accepted.
Line 95	3	Comments: It is stated that “parabens display similar affinity for the 2 types of human oestrogen receptors”. However, a recent publication showed evidence that methyl- and propylparaben exhibited ERβ-agonistic activity at lower concentrations than those inducing ERα-agonistic transcriptional activity in a luciferase reporter gene assay in ERα and ERβ transfected CHO-K1 cells (Watanabe et al, 2013, Food and Chemical Toxicology 57: 227-234). Proposed change (if any): Update the paper with the information from the	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		above mentioned reference.	
Line 106	3	Comments: Lack of actual data from the referred reference (Boberg). Proposed change (if any): Add the oral NOEL of 800 mg/kg/day for the uterotrophic effect in immature rats (Routledge et al., 1998) for methylparaben and the oral NOEL of 100 mg/kg/day for the uterotrophic effect of methyl- and propylparaben and of a mixture (equal amounts) of methyl-, ethyl- and propylparaben (Hossaini et al., 2000) in immature mice.	Partly accepted. Since patients will be exposed to parabens via oral route, it seems adequate to report that negative results were obtained with those compounds administered orally to rodents. However, reporting the results obtained with the mixture of methyl-, ethyl-, and propylparaben may not be relevant since - Ethylparaben is not covered by this document - The dose level of each compound included in the mixture (33 mg/kg) is low, especially when compared to oral NOELs determined by the same authors in the same experimental model (100 mg/kg for methyl- and propylparaben, 1000 mg/kg for ethylparaben). Therefore, reporting this result could be misleading.
Lines 106-115	3	Comments: The actual tested doses, effective doses and NOELs are not included. Proposed change (if any): Include the above mentioned information, only for the two relevant parabens. Information regarding other parabens should be moved to the separate text as proposed in comment 3.	Partly accepted. Most studies were performed by sc. administration, therefore the relevance of such data (dose levels) may be low. For positive results (obtained only after sc dosing), ED_{50} values will be added (see above). As indicated above, the oral NOELs were added to the text.
Line 131	7	Comments: Additional data on oestrogenic activity are available in the publication by Shaw & deCatanzaro, Reprod Toxicol. 2009 Jul;28(1):26-31.	Accepted. (Shaw and deCatanzaro 2009 already taken into consideration).
Lines 141 - 145	6	Comments: We suggest reconsidering the presented values of	Accepted. According to the publication of Oishi (2002b), the dose of 1%

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		LOAEL in the following text. It seems incorrect: *A decrease in the testicular and epididymal quantity of spermatozoids was observed with a lowest-observed adverse effect level (LOAEL) of 0.01% corresponding to an average propylparaben intake of 12.4±3 mg/kg/day. A dose dependent decrease in serum testosterone concentration was significant at a dose of 1%, corresponding to 125±30 mg/kg/day propylparaben (Oishi, 2002b).*	corresponds actually to an average propylparaben intake of 1290±283 mg/kg/day.
Line 145	7	Comments: Comment: It is recommended that the study by Oishi needs a more detailed discussion since some may assert that it has equal standing to the recent more comprehensive study, being from an "independent" source and providing a much more conservative metric (low dose as LOAEL). [Moreover, data from the Oishi study have been cited in a couple of EPARs to support a requirement to reformulate drug products in order to remove propyl paraben: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002022/WC500124643.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000863/WC500050341.pdf]. In fact the Oishi study on propyl paraben has multiple deficiencies, as pointed out in the various	Not accepted. **Specific comments** The reflection paper already reports that the lack of TK investigation in the Oishi study is a major limitation. It is also mentioned that the results of the Gazin et al study are more reliable since it used a more extensive design in a GLP environment. Of note, the reflection paper was updated with results of a new GLP study performed by an EFPIA member using much younger rats at initiation of treatment. The lack of effect on development of the male rat reproductive tract confirms the results of Gazin et al. Overall, two GLP-compliant and well-designed studies are now available. Both of them did not confirm the results obtained previously in the study conducted by Oishi (2002) whose major limitations were adequately reported. **General comments** This is out of the scope of this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		assessments by EFSA and SCCS. These include: • Failure of the author to provide raw data following a request by EU authorities; • Proposed mechanism not supported by the data; • Outlier concurrent control values, particularly for DSP and testosterone, not consistent with literature data (and data from other Oishi studies); • Lack of dose-response for several key parameters; • Absence of TK data; • Lack of clarity on GLP status. The lack of dose response on key parameters should have rung alarm bells since this is often a strong indication of aberrant concurrent control values. This phenomenon, and other issues that can cloud judgements on distinguishing adverse from non-adverse effects, are discussed in detail by Lewis et al: http://tpx.sagepub.com/content/30/1/66.full.pdf The following five issues are considered to be of greatest importance when deciding whether an effect is truly adverse: 1. there is no obvious dose response: 2. it is due to finding(s) in one or more animals that could be considered outlier(s): 3. the measurement of the endpoint under evaluation is inherently imprecise;	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		4. it is within normal biological variation—within range of historical control values or other reference values; 5. there is a lack of biological plausibility. A difference is inconsistent with class effects, mode of action, or what is otherwise known or expected of the test substance. Had this kind of evaluation been applied to the Oishi study – as should have been the case (both EFSA and JECFA were remiss in not analysing the Oishi report more carefully) it is extremely doubtful whether propyl paraben would have been effectively withdrawn as an approved food additive in the EU. [FDA has not banned propyl paraben and in 2006 EPA indicated that confirmatory data were required before regulatory action could be justified.] Proposed change (if any): **Specific**: Remarks should be included demonstrating the many deficiencies of the Oishi paper and demonstrating is lack of plausibility. **General**: • SWP should consider including the criteria spelled out by Lewis et al in the Critical Assessment Report template so that preclinical assessors are in a better position to make judgements on the appropriateness of a particular NOAEL. • A raw data audit should be conducted on any relevant publication from which a NOAEL has been derived *before* this NOAEL	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is used for regulatory purposes	
Lines 146-148	2	Comments: More information should be provided on the referred study. Proposed change (if any): Recently, an 8-week postweaning juvenile toxicity study initiated and sponsored by the French Health Product Safety Agency (AFSSAPS)[1] was conducted with the aim to confirm these conclusions ~~another GLP compliant study has been undertaken with a similar but more extensive design~~. Propylparaben was given by oral gavage to 4 main groups of 20 male Wistar rats at nominal doses of 3, 10, 100 or 1000 mg/kg/day for 8 weeks starting from post natal day (PND) 21.	Partly accepted. Any reference to the sponsorship of the study by the Afssaps is not deemed necessary. However, it is agreed to report here that the aim was to reproduce the findings of Oishi (2002b). The wording below is proposed: Recently, a GLP-compliant juvenile toxicity study was undertaken with a similar but more extensive design with the aim to confirm these conclusions. Propylparaben was given by oral gavage to 4 main groups of 20 male Wistar rats at nominal doses of 3, 10, 100 or 1000 mg/kg/day for 8 weeks starting from post natal day (PND) 21.
Line 162-163	2	Comments: As explained above, the Gazin et al has been recently published. Proposed change (if any): The toxicokinetic data showed that the duration of exposure between dosing intervals was short; non-conjugated propylparaben was detected up to at the most 1 h (after 8 weeks dosing) - 4 h (data after first dose) after dosing in the highest dose	Partly accepted. It is agreed to add a sentence to give a conclusion on this study. It should notably indicate clearly that findings reported by Oishi (2002b) were not reproduced. As regards the wording, it is rather proposed to rely on the text of Gazin et al (2013). "The toxicokinetic data showed that the duration of exposure between dosing intervals was short; non-conjugated propylparaben was detected up to at the most 1 h (after 8 weeks dosing) - 4 h (data after first dose) after dosing in the highest

[1] Became the National Agency for the Safety of Medicines and Health Products - Agence nationale de sécurité du médicament et des produits de santé (ANSM)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		group. If total concentrations (non-conjugated and a sulphoconjugate of propylparaben) are considered, exposure was evident for up to 4h (after 8 weeks dosing) - 8 h (data after first dose). The nominal dose of 1000 mg/kg/day was the no 162 observed effect level. No consistent pattern of effects on testis and epididymides and no dose-relationship were observed. Taken together, findings were not suggestive of an effect of propylparaben on male reproduction. The study therefore concluded that once daily oral (gavage), administration of propylparaben to male Wistar rats at nominal doses of 3, 10, 100 and 1000 mg/kg between 3 and 11 weeks of age was without any effects on general health nor reproductive parameters in any group. (Gazin V. et al, ~~submitted for publication~~ publication online).	dose group. If total concentrations (non-conjugated and a sulphoconjugate of propylparaben) are considered, exposure was evident for up to 4h (after 8 weeks dosing) - 8 h (data after first dose). In conclusion, although exposure to propylparaben was observed following gavage administration to rats, there was no evidence of any effect on male rat reproductive organs. This toxicity study conducted according to GLP in an appropriate and statistically robust manner failed to reproduce the effects on endocrine functions observed by Oishi (2002b). The nominal dose of 1000 mg/kg/day was the no observed effect level (Gazin et al, 2013)."
Lines 164-180	3	Comments: Some details regarding methyl- and propyl paraben might be added. Proposed change (if any): IC50 values observed for methyl and propylparaben might be added (4.6 - 5.6 x 10^{-5} M and 1.9 – 1.7 x 10^{-5} M (ERα - ERβ) respectively).	Not accepted. The IC_{50} values determined by Vo et al (2010) were already reported and tabulated in the section on estrogenic activity.
Lines 164-180	3	Comments: The in vivo results in this study showed several significant effects, also at the high methyl paraben dose. The effect of propyl paraben on uterus	Partly accepted. Since the publication of the draft reflection paper, a GLP-compliant juvenile toxicity study was performed and the results were submitted by BMS. Juvenile male and female rats were

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		thickness was only significant at the highest dose, but a trend was visible at lower doses. All tested parabens at all doses (62.5 – 1000 mg/kg) appeared to cause a decreasing trend in corpora lutea to a level intermediate between negative control and ethinylestradiol. This effect appeared to correlate with tail length, but was not significant for methyl, ethyl, propyl paraben, except for the mid dose of methyl paraben. Considering the large number of comparisons, it is possible that some of the significances are false-positive results, however the effect on corpora lutea appears rather consistent for all tested parabens. Therefore it is difficult to conclude with certainty that the NOEL of 250 mg/kg/day is a real NOEL. It seems that more data are needed to confirm this NOEL. In addition, it is noted that NTP has planned a testing program of the toxicity of propyl paraben as following: Planned Carcinogenicity/Toxicity: 14-Day Modified One-Generation - GD 6 to PND 28 Dose Range Finding (Gavage): Dose Range Finding in rats. - Conventional Teratology (Gavage) in rats - F0 Generation (Gavage) in rats. - Fertility Assessment (Gavage) in rats. - 90 days Subchronic (Gavage) in rats Special Studies	treated from PND4 to PND90; this treatment duration covers all subsets of the paediatric population, and largely encompasses the treatment duration used by Vo et al (2010). A NOEL of 100 mg/kg/day was determined based on significant findings reported in female rats at 1000 mg/kg/day (accelerated onset of puberty, increased uterus weight). A revised PDE of 2 mg/kg/day was calculated and was considered as relevant for the whole paediatric population and adult patients.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- 5 days Uterotrophic Assay (Gavage) in rats, Uterotrophic Assay plus Liver (Hybrid) Genetic Toxicology - Salmonella (810084) Completed: Equivocal - Salmonella (A72946) Completed: Negative Toxicogenomics - Microarray Analysis (Gavage) in rats <u>Proposed change (if any):</u> A provisional PDE may be established, which is reassessed by the time more relevant results are available. Find out when the results of the NTP studies are to be expected. More studies regarding juvenile effects may be needed, for a more reliable NOEL.	
Lines 164-180	6	Comments: We suggest to complement this section by additional papers concerning the influence of parabens on female reproductive system: According to the results presented by Ahn et al. (2012) propylparaben (62,5-1000 mg/kg) stimulated anti-Mullerian hormone (AMH) mRNA expression and consequently inhibited the early phase of folliculogenesis in the ovaries of neonatal female rat. The results suggested that exposure to	Not accepted. Ahn et al (2012) report findings suggesting that propylparaben (not methylparaben) suppress the transformation of primordial follicles into early primary follicles in rat ovaries. In this study, rats were treated s.c. from PND1-7. In rats, primordial follicles are formed postnatally, by 3 days after birth, and secondary follicles are found by 7 days of age (McGee and Hsueh, 2000). In the newly submitted study performed by an EFPIA member, dosing was initiated in 4-day old female rats. Therefore, exposure to propylparaben occurred likely during the transformation of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		parabens during neonatal periods may disrupt folliculogenesis and cause abnormality in the female reproductive system due to imbalanced steroid regulation. In another study authors assessed the impact of parabens upon early gestation (Shaw 2009). Propylparaben was subcutaneously administered to inseminated CF-1 mice on gestational days 1-4. Dams were sacrificed on gestation day 6 and the number of implantation sites was counted. Propylparaben had no impact on the number of implantation sites observed. In contrast, administration of 500 ng/animal/day of 17-beta-estradiol terminated all pregnancies. These data indicate that the oestrogen-sensitive period of implantation is not vulnerable to paraben exposure, however the doses of propylparaben were rather low (0.05 to 35 mg/animal/day). There is limited number of epidemiologic studies assessing female reproductive health effects in relation to paraben exposure. However, evaluation of the association of urinary paraben concentrations with markers of ovarian reserve in a prospective cohort study of women suggested that propyl-paraben may be associated with diminished ovarian reserve (Smith 2013). • Smith KW, Souter I, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, Hauser R.	primordial follicles into early primary follicles. However, there was no treatment-related effect on estrous cyclicity, mating and fertility, maternal performance, and histopathology of reproductive tract organs in these animals. Overall, these new findings would not confirm those of Ahn et al (2012). Further, it is noted that the number of primary follicles was not significantly different in control and propylparaben-treated animals in the Ahn et al (2012) study. In addition, transformation of primordial follicles into early primary follicles occurs during fetal life in humans, by 20-24 weeks of gestation (McGee and Hsueh, 2000) so that direct extrapolation of these findings to human neonates may not be relevant (e.g. parabens would be significantly metabolised by the mother before reaching the fetus). Shaw and de Catanzaro (2009) administered sc propylparaben to CF-1 mice from GD1 to GD4; the top dose reached 40 mg/animal/day, i.e. approximately 1000 mg/kg/day based on a mean body weight of 39.6 g (as indicated in the publication). They report a lack of significant effect on implantation sites counted on GD6 vs. controls. In a previous experiment investigating the effects of butylparaben, E2 (positive control) administered at 500 ng/animal/day according to the same schedule terminated all pregnancies but implantation sites were not counted on GD6 (females were allowed to deliver their pups). The lack of similar comparison of effects of propylparaben vs. E2, the fact that treatment did not span the whole implantation period (up to GD6), and the low number of animals used (5/7 per group) cast doubts on the relevance of the results.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Urinary Paraben Concentrations and Ovarian Aging among Women from a Fertility Center. Environ Health Perspect. 2013 Aug 2. • Ahn HJ, An BS, Jung EM, Yang H, Choi KC, Jeung EB. Parabens inhibit the early phase of folliculogenesis and steroidogenesis in the ovaries of neonatal rats. Mol Reprod Dev. 2012 Sep;79(9):626-36 • Shaw J, de Catanzaro D. Estrogenicity of parabens revisited: impact of parabens on early pregnancy and an uterotrophic assay in mice. Reprod Toxicol 2009; 28: 26-31.	
Line 177	7	Comments: A raw data audit should be performed on the Vo et al publication, and the NOAEL determined on the basis of the factors discussed by Lewis et al, 2002.	Not accepted.
Lines 181-264	3	Comments: Are there also medicines containing a mix of methyl paraben and propyl paraben? Considering the probably common mechanism of action, their effects could be expected to be additive. Should there be a limit for the sum of the two? <u>Proposed change (if any):</u> Discuss combination exposure and implications for the ADI in section 3.	Not accepted. It is stated in the introduction that combinations of methylparaben and propylparaben are used in oral pharmaceutical preparations. Although there is no data available with such a combination, the reflection paper concludes that "based on the totality of the in vitro and in vivo data, it can be concluded that methylparaben seems to be devoid of adverse effects on reproduction and development". Therefore, an additive effect seems unlikely.
Lines 181-	3	Comments:	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
264		A patient may use several oral formulations containing parabens, either as preservative or as active ingredient (see comment 15). A possible additive exposure from combined exposure to parabens should be taken into account, or at least discussed. In addition, patients may ingest parabens from the daily diet and/or absorb them from cosmetics. It should be assessed whether the overall exposure remains low enough. <u>Proposed change (if any):</u> Add discussion regarding possible additive exposure to parabens from different sources as mentioned above.	The use of methyl and propylparaben as antimicrobial preservatives in human medicinal products should be justified, and avoided if possible. Their concentrations should be as low as possible (CHMP/QWP/396591/2006). Potential additive sources of exposure are the food and cosmetics, and the data do not suggest a high risk related to additivity of exposures as detailed below. <u>Food</u> A full group ADI of 10 mg/kg was established by the EFSA for the sum of methylparaben and ethylparaben. The use of methylparaben at up to 0.2% in human medicines would correspond to a maximal intake of 2.8 mg/kg/day (worst case scenario) and is within the EFSA ADI, and not at its upper level of the ADI. It is also reminded that methylparaben “seems to be devoid of adverse effects on reproduction and development” (see above). From 2006, propylparaben is no more allowed as a food additive. <u>Cosmetics</u> A conservative value of 3.7% dermal absorption was used by the SCCS to determine safe, acceptable levels of propyl and butylparabens in cosmetic products. Furthermore, propylparaben and butylparaben should not be used in cosmetic products intended to be applied on the nappy area of children below 3 years. Therefore, any additive exposure from cosmetic products should be limited.
Lines 206-	3	Comments:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
209		Comment 16: It would be convenient for the reader if the maximum possible dose of methyl paraben would be added here. Proposed change (if any): Add the maximum dose of methyl paraben from an oral medicinal formulation.	
Lines 206-209	5	Comments: The statement that the use of up to 0.2% methyl parabens is consistent with the EFSA ADI does not accurately reflect the market usage of methyl parabens Proposed change (if any): Inclusion levels to be amended to reflect market situation (Reckitt Benckiser have proprietary data that can be shared under confidentiality to support the above recommendation).	Not accepted (see comment on this issue in section 1).
Line 214	7	Comments: Effects noted in the Oishi publication lack plausibility owing to aberrant concurrent control data, etc, as discussed above. Proposed change (if any): Include additional commentary on the Oishi data.	Not accepted (see above).
Lines 215-217	2	Comments: Editorial change Proposed change (if any):	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Such effects were not ~~reproduced~~ confirmed in a recent GLP-compliant study (Gazin et al), the design of which is more extensive. Hence, no effects on male reproduction parameters were seen following 8 weeks daily oral administration of doses up to 1000 mg/kg, to male rats from 3-11 weeks of age.	
Lines 218-219	2	Comments: Editorial change Proposed change (if any): Different oral administration methods were applied in the Oishi (2002b) study and the ~~recently conducted~~Gazin (2013) study; via the diet and gavage administration, respectively.	Accepted. (Even though the proposed wording was slightly modified to take into account the new study submitted by BMS).
Lines 219-234	2	Proposed change (if any): From the Oishi (2002b) study, there are no data on the systemic exposure of the animals, which is a major limitation. Toxicokinetic data from the ~~recently conducted~~Gazin (2013) study showed that the duration of exposure between dosing intervals was short. Although ~~T~~there are no adequate human data on the pharmacokinetic profile of orally administered propylparaben, e.g., following intake of a propylparaben containing pharmaceutical, the Gazin et al study includes gavage administration in order to more closely mimic the oral administration of propylparaben in pharmaceuticals. ~~However, b~~Based on data available, it can be anticipated that the systemic exposure to propylparaben following	Partly accepted. Most changes were taken into consideration. However, the last sentence was not accepted since it is reported earlier that findings of Oishi (2002b) were not confirmed by Gazin et al (2013) and that the new study submitted by BMS did not evidence any effect on the developing male reproductive tract.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		oral intake, at least in adults, is short. In addition, the metabolites are not considered likely to have endocrine disrupting properties, and consequently, the exposure to propylparaben is the main focus. ~~While it is likely that dietary administration of propylparaben, as in the Oishi study, could have resulted in a more prolonged and even systemic exposure to propylparaben, gavage administration, as in the recently conducted study, more closely mimics the clinical setting following oral administration of a medicinal product.~~ In addition due to the design and GLP conditions of the Gazin et al study, its results are considered to be more reliable. Thus, for oral administration of those pharmaceuticals which result in short (hour) daily (but repeated) exposure to propylparaben, the data from the newly conducted juvenile toxicity study provide reassurance regarding lack of risk for endocrine disrupting effects for propylparaben. In fact, there was no evidence of any treatment-related effect on testicular and epididymal weights or on sperm count and motility data and on the levels of the measured hormones (LH, FSH and testosterone).	
Lines 227-234	3	Comments: It is assumed that gavage treatment in animal studies more closely mimics clinical exposure. For medicines used once or twice per day this appears a reasonable assumption. However, some	Not accepted. It is acknowledged that some variability may occur when extrapolating an ADI derived from a gavage study to the use of a slow release oral formulation / oral formulation used 6-8 times a day. However, it is assumed that the ADIs derived from studies

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		medicines are used more often on a day and slow release formulations will also slowly release parabens. Some oral formulations are used 6-8 times a day. In these cases exposure will be more evenly distributed over a day. This possibility should also be discussed, is the ADI derived from the Gazin and the Vo studies also valid for these cases? Or should there be a limitation regarding paraben content of medicines used more often c.q. slow release formulations. <u>Proposed change (if any):</u> Discuss also the safety of the approach for medicines used more often per day and slow release formulations (are there data concerning content en total daily dose of this type of formulations, it might be helpful to relate the text to examples of actual maximum doses).	performed by gavage are considered as valid for all oral human medicinal products, since: • The PDE was derived taking account safety factors which may cover this variability, at least to some extent. It represents also an acceptable daily intake over lifetime exposure, whereas drugs administered 6-8 times per day may not probably be prescribed for such a duration; • Alternative dosing methods such as dosing via the diet also yield some variability due to e.g. i) the unknown delay between compound intake and blood sampling (rodents eat mainly during the night and blood may be sampled in the morning or afternoon) which may complicate TK interpretation, ii) less precise knowledge of administered doses.
Line 237	7	Comments: Clarification required as to whether 250 mg/kg/day is a NOEL or NOAEL.	According to Vo et al (2010), a significant effect on uterine thickness was reported at 1000 mg/kg/day only. Effects on corpora lutea were not considered as significant. Therefore, the dose of 250 mg/kg/day is a NOEL.
Lines 250-264 and 301-311	1	Comments: New data has recently been gathered and made available for review by a member company (BMS), to address the aforementioned caveat (i.e. excluding children below 2y of age regarding the PDE for propylparaben). In view of conflicting reports on estrogenic activity or propylparaben, BMS designed and conducted a	Accepted (although a lack of estrogenic effect could not be ascertained in high dosed females, as stated in section 1).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		comprehensive evaluation of propylparaben in juvenile rats, in two parts (summary enclosed as slide deck). The first was a study to determine whether administration of propylparaben by oral gavage from early neonatal life to 3 months of age was associated with estrogen-mimetic effects on organs and tissues of the reproductive tract in juvenile Sprague-Dawley rats, both male and female. No evidence of paraben-related effects was found on any measures of reproductive function in males or females at any dose tested (including external landmarks of sexual maturation, weights of reproductive tract organs, estrous cyclicity in treated females, fertility in either sex, and histopathology). The second part was a direct assessment of the effects of propylparaben administered by oral gavage on uterine wet weights in juvenile rats. There was no effect of propylparaben on uterine weights at any dose administered. From the first study it was known that paraben AUC values were low, relative to metabolite levels, demonstrating rapid conversion from parent to PHBA; as well as rapid sulfation of both propylparaben and PHBA.) Importantly, the oral route of administration will be used for pharmaceutical preparations containing propylparaben for its antimicrobial activity. Considered together, these data support the use of propylparaben as an antimicrobial in oral pharmaceutical formulations for use from the neonatal period through 18 years of age.	

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td> 
EMA Update on BMS Propylparaben Study

Proposed change:
Based on this new data EFPIA strongly recommends deleting the aforementioned caveat (i.e. excluding children below 2y of age regarding the PDE for propylparaben).</td><td></td></tr>
<tr><td>Lines 250-258</td><td>7</td><td>Comments:
An abstract from the attachment is provided in relation to carboxylesterase activity at different stages of rat/human development. (More detailed information is shown in the annexes to the attachment):

It is of considerable interest to be able to evaluate the development of CE activity in the rat and in human. Relevant publications are those by Karanth & Pope, Toxicol Sci, 2000, and by Pope et al, Regul Toxicol Pharmacol, 2005 (Annex 6). Confirmatory data are provided by Moser et al, Toxicol Sci, 1998 (Annex 7). CE activity in neonatal and juvenile rats as a % of that in mature rats is shown in Table 1 (based on data from Karanth & Pope).

Table 1: CE Activity in Neonatal and Juvenile Rats

<table><tr><th>Age of Animals</th><th>Plasma CE (% of adult level)</th><th>Hepatic CE (% of adult level)</th></tr><tr><td>Neonatal (PND 7)</td><td>25</td><td>10</td></tr><tr><td>Juvenile (PND 21)</td><td>40</td><td>55</td></tr></table></td><td>Not accepted.
Pope et al (2005) clearly report some limitations of their study, such as the low number of tissue samples available from individuals ≤ 2 years of age. In addition, others have reported that the activity and/or expression of human carboxylesterases are higher in adults than in children (Yang et al 2009, Shi et al 2013, Zhu et al 2009).</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Adult rats were at PND 90 In the 2005 publication Pope et al report that, by contrast, in humans CE activity reaches adult levels two months after birth. Hepatic CE activity in humans changes relatively little during postnatal maturation. Since CE activity seems to be critically relevant to the toxicity profile of the parabens, data from neonatal rats, and possibly from juvenile rats, may not be relevant to human children or adults. If CE activity were saturated in a neonatal/juvenile rat model one would expect to see a "break-point" in terms of the PP dose-response curve in relation to potential adverse effects on male fertility in the juvenile rat. This *may* be the case for reductions in serum testosterone but not for DSP. A good example of the impact of low CE activity on toxicity in immature rats is provided by oseltamivir phosphate which is clearly more toxic in PND 7 rats compared to PND 42 rats (in terms of single-dose toxicity). The increased toxicity (mortality and morbidity) in PND 7 rats (LOAEL 500 mg/kg) compared to PND 42 rats (NOAEL ≥ 1000 mg/kg) is ascribed to incomplete hydrolytic conversion of the parent drug (ethyl carboxylic acid ester) to the active form (carboxylic acid) (Annex 7). The LOAEL dose is equivalent to 1.22 mmole/kg whereas doses of PP used by Oishi were 0.06, 0.55 and 5.6 mmole/kg/day for 4 weeks, suggesting that a break-point *might* occur at the high dose if CE activity were limiting. Development of CEs in skin are discussed in a recent SCCS report: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_132.pdf Proposed change (if any): The data on CE activity are considered to be reassuring regarding the safety of oral propyl paraben in infants down to age 2 months, at which time plasma and hepatic CE activity reaches adult levels.	
Lines 254-258	2	Proposed change (if any): Thus, it is not possible to conclude that the data from ~~the new study~~the Gazin et al study are fully	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reassuring for this low age group. Regarding estimation of an acceptable amount of propylpraben that can be included in an oral medicinal product, margins cannot be estimated based on toxicokinetics, given the lack of adequate human data.	
Lines 259-264, and footnote	7	Comments: Use of NOEL and/or NOAEL is confusing and ambiguous. In fact ICH Q3C uses NOEL not NOAEL, but based on interpretation of ICH Q3C guidance for solvents and for metals (in ICH Q3D) it appears that NOEL and NOAEL are considered equivalent. PDEs should be cited as mg/kg or mg, since the unit of time is already embedded in the name of the metric (ie permitted *daily* exposure). Proposed change (if any): Clarifications required and possibly re-examination of Vo et al paper to distinguish between NOEL and NOAEL for propyl paraben.	Partly accepted. According to ICH Q3D, the F5 factor should be set at 1-5 when a NOAEL is used instead of a NOEL. Therefore, they are not considered equivalent. It is stressed in the guideline that “for most elements the NOAEL was used to set the oral PDE, using a F5 of 1, as the studies did not investigate the difference between a NOAEL and NOEL and the toxicities were not considered “adverse” at the dose selected for determining the PDE”. A footnote was corrected since it reported that PDE was calculated based on a NOAEL value based on ICH Q3C. It reports now that this is based on a NOEL value.
Lines 278 - 280	3	Comments: Please specify this investigation with more information, including the source (e.g. registration data on composition of human oral medicinal products approved in the EU?). <u>Proposed change (if any):</u> Please update with the information.	Accepted.
Lines 280 -	3	Comments:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
282		Please add the source of this information (e.g. SPCs of human oral medicinal products approved in the EU?). Proposed change (if any): please update with the source.	
Lines 283-286	5	The ranges for Methyl and propylparabens do not reflect actual market usage Proposed change (if any): Inclusion levels to be amended to reflect market situation with associated update of posology and risk assessment (Reckitt Benckiser have proprietary data that can be shared under confidentiality to support the above recommendation).	Not accepted (see comment on this issue in section 1).
Lines 290-292	5	Comments: The ranges for Methylparabens do not reflect actual market usage Proposed change (if any): Inclusion levels to be amended to reflect market situation with associated update of posology and risk assessment (Reckitt Benckiser have proprietary data that can be shared under confidentiality to support the above recommendation). Proposed change (if any):	Not accepted (see comment on this issue in section 1).
Lines 310 - 311	6	Comments: As it was mentioned in the analysed document, in oral pharmaceutical formulations propylparaben is	Not accepted. The text mentions already that parabens should be used at the lowest feasible level, or even that their use should be avoided

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		applied with concentrations generally ranging from 0.02% to 0.06%, and a concentration of 0.06% propylparaben would correspond to a maximal oral intake of approximately 50 mg/day (1 mg/kg/day). In the section *General consideration* we can read: "***Wherever possible the use of these substances (parabens) should be avoided***, *particularly in case of paediatric formulations.* ***The concentration used should be at the lowest feasible level***" while further in the section *Specific consideration* there is the summarizing sentence: *PDE value of 5 mg/kg/day can be calculated for the use of propylparaben in adults and children older than 2 years with mature metabolic capacity*. In the context of data mentioned above this sentence suggests that medicinal products containing even higher concentration of propylparaben than 0.06% is safe. Taking into account the limited number of scientific data concerning the safety of propylparaben, it seems rather reasonable to restrict its concentrations in medicinal products to minimum until more data will be available.	wherever possible.
Lines 301–311	4	Comments: • While it is true there is some uncertainty around the nature and maturity of the metabolic routes of parabens in very young children, there seems to be clear evidence of the critical contribution of human carboxylesterases in the literature. There is a growing body of knowledge in the field of hCEs	Not accepted. As mentioned already, a new juvenile toxicity study was conducted and the results were submitted by BMS. Based on the age of rats involved in this study, it is considered that this study is relevant for patients aged 0-2 years. A NOEL could be determined in this study, and a PDE value of 2 mg/kg/d could be calculated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and how they mature through childhood. We believe there is sufficient evidence in the literature to suggest that activity of these enzymes is present at birth, increases steadily through the first year of life, being approximately at 50% of adult levels of activity by the age of 1 year[5,6,7].  Zhu et al 2009.pdf 5. Zhu et al 2009  Yang et al 2009.pdf 6. Yang et al 2009  Shi et al 2013.pdf 7. Shi et al 2013 • In addition, on lines 246–247, it is stated that the male reproductive system is not more sensitive in children below 2 years of age, and this is supported by the literature. Additionally, there is evidence in the literature[8] that administration of propylparaben to prepubertal female rats does **not** significantly affect circulating hormone levels, reproductive organ weights or the number of corpora lutea or cystic follicles, although it is noted that myometrial hypertrophy is observed at a very high dose. Therefore, the lack of animal data	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should not be considered a major impediment to the assessment of risk for this population. . Vo TTB, et al. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model (2010): *already included in the references at the end of the draft guideline (lines 376-377, last reference)*. • We believe that the evidence of involvement of hCEs in the metabolism of parabens and the associated knowledge of their expression and activity in children below 2 years could allow the conclusion that children between the ages of 1 and 2 would have a negligible risk of exposure to low levels of parabens esters. We therefore propose a lower PDE for propylparaben in children aged between 1 and 2 years old of 2.5 mg/kg/day based upon the estimate that the clearance of parabens in children older than >1 year is at least half that of older children. There is evidence in the literature that the elimination of the major hydrolytic metabolite of parabens esters (4-hydroxybenzoic acid) is mostly via renal excretion with or without conjugation with sulphate or glucuronide[2,9,10]. As glomerular filtration rate reaches adult values by the end of first year of life, and levels conjugation enzyme activity in children of 1 year is	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		approximately equivalent to adults, there is no expectation that this metabolite will lead to any safety concerns.  Abbas et al 2010.pdf 2. Abbas et al 2010  Wang et al 2013.pdf 9. Wang et al 2013  Soni et al 2002.pdf 10. Soni et al 2002 Proposed edits to the text: ~~'For children below 2 years a PDE for propylparaben cannot be determined because of the uncertainty related to the maturation of the enzymes that metabolize propylparaben as well as the limitation of the available animal data corresponding to the youngest children~~. **Based on what is known about the metabolic capacity and maturation of carboxylesterases in children between 1 and 2 years of age, it is possible to determine an appropriate PDE for this group**. ~~However~~ ~~s~~**S**afety margins identified in adults and children older than 2 years are currently reassuring. ~~Nevertheless, for children below 2 years further exposure data for propylparaben are needed.~~ The use of a propylparaben containing	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		formulation for the very young could be justified on a case-by-case basis from a benefit/risk perspective, weighting the need for treatment against the potential risk. This assessment should take into account several factors such as the posology and concentration of propylparaben, the treatment duration, the severity of the disease and availability of alternative treatments. A PDE value of 5 mg/kg/day can be calculated for the use of propylparaben in adults and children older than 2 years with mature metabolic capacity. **For children aged between 1 and 2 years old, a lower PDE for propylparaben of 2.5 mg/kg/day should be applied, based on the available literature about the metabolic capacity and maturation of carboxylesterases in children below age 2 years**.'	
Line 338	2	Comments: The study entitled "Oral propylparaben administration to juvenile male Wistar rats did not induce" toxicity in reproductive organs was published online in the official journal of the Society of Toxicology, Toxicological sciences on 25 September 2013. Proposed change (if any): Gazin V., Marsden E., Briffaux J-P (2012), Propylparaben: 8-week postweaning juvenile	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		toxicity study 335 with 26-week treatment free period in male Wistar rat by the oral route (gavage) Poster SOT Annual 336 Meeting San Francisco USA - Abstract ID 2359*327 337 Gazin V., Marsden E., Marguerite F. (2013), Oral propylparaben administration to juvenile male Wistar rats did not induce toxicity in reproductive organs. Toxicol. Sci. First publication online: September 25, 2013 Guideline on Excipients in the dossier for application for Marketing Authorisation of a Medicinal Product 338 (EMEA/CHMP/QWP/396951/2006).Hoberman AM, Schreur DK, Leazer T, Daston GP, Carthew P, Re T 339 Lorets L and Mann P (2008). Lack of effect of butylparaben and methylparaben on the reproductive 340 system in male rats. Birth defects research. 83(2):123-33	